REMARKS:

Minor changes are made to this specification. Claims 8-12 are amended; marked up versions of the amended claims are attached hereto pursuant to 37 C.F.R. § 1.121(c)(ii). Claims 8-12 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Objections to the Specification

The Specification stands objected to under 35 U.S.C. § 112, first paragraph. The Office contends that the Specification is "replete with terms, which are not clear, concise and exact." Specific examples cited by the Office are, e.g. p. 5, lines 6-7, "but brought no good solution", and line 17, "from extracted a tooth of mammalia'"; p. 11, line 9 and p. 17, line 23, "removed not remaining using a scaler..." The examiner has suggested that the Applicant carefully revise the Specification. In response, Applicant has revised Specification to correct the passages cited by the Office.

Applicant notes that 35 U.S.C. § 112, first paragraph, reads *in toto* as follows:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. (Emphasis added).

Applicant notes that the first paragraph of § 112 only requires such "full, clear, concise and exact terms" as to "enable any person skilled in the art... to make and use" the invention. Applicant notes that the first paragraph does not require perfect English. Applicant will, of course, cooperate with the Office in correcting any errors of which Applicant becomes aware.

Claim Objection

Claim 12 is objected to because the Office contends that, at the end of claim 12, the second period (i.e. ".") should be deleted. In response, claim 12 has been amended in the manner suggested by the Office. Withdrawal of the objection is respectfully requested.

Claim Rejections– 35 U.S.C. § 112

Claims 8-9 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office contends that the Specification, while enabling for CCTF from the cementum or precementum obtained from a bovine tooth, does not reasonably provide enablement for preparation of the CCTF from any mammalian tooth with these properties. Claims 8-9 and 12 are amended. Applicant respectfully traverses the rejection as to the amended claims.

Applicant's Specification at p. 7, line 7- p. 11, line 2 is directed to a glycoprotein derived from the teeth of Mammalia in general and is not limited to glycoprotein derived from the bovine tooth. The Office appears to reject the present claims "because the preparation and/or properties of said CCTF from the cementum or precementum from any other mammal tooth has not been exemplified." However, the MPEP specifically states that "the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure..." MPEP 2164.02. Thus, Applicant's inclusion of working examples of CCTF derived from bovine tooth is an insufficient basis for rejecting claims 8-9 and 12. Further, the office has provided no other basis for its determination that one of ordinary skill in the art could not make or use the claimed invention without undue experimentation. As such, withdrawal of the rejection is respectfully requested.

Claims 8-12 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Specifically, the office contends that the phrase, "consisting essentially of a factor with a molecular weight" at line 3 of claim 8 render claim 8 indefinite since this claim as presented does not clarify whether the molecular weight referred to is that of CCTF, or of another factor which is a component of CCTF. Appropriate correction is being required by the Office. Claim 8 is amended. As amended, claim 8 is directed to "a purified gingival fibroblast chemotactic factor having a molecular weight of 67000 ± 1000 measured by SDS-PAGE." As such, it clear that the molecular weight is that of CCTF. Withdrawal of the rejection is respectfully requested.

Claim 12 further stands rejected under 35 U.S.C. § 112, second paragraph, because the Office contends that the recitation "precementum- and/or cementum-derived" at line 2 of claim 12 is unclear as well as confusing, and therefore, indefinite because the word "derived" does not clearly define as to how a similar material should be to the base material to be called a derivative." The examiner suggests that applicant delete the phrase, "precementum- and/or cementum derived" at line 2 of claim 12 and insert the phrase --obtained from precementum and/or cementum"-- after the word "(CCTF)". In response, claim 12 has been amended in the manner suggested by the Office. Withdrawal of the rejection is respectfully requested.

Claim Rejections– 35 U.S.C. § 102

Claims 8-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Ogata et. al. (Comp. Biochem. Physiol., Vol. 116B (3): 359-365, 1997.) Claims 8-12 are amended. Applicant respectfully traverses the rejection as to the amended claims.

The present invention is a directed generally to a chemotactic factor derived from the precementum and/or cementum of mammal teeth, a process for purifying the claimed factor and a drug using the claimed chemotactic factor. The

chemotactic factor of the present invention has a molecular weight of 67 kD on SDS-PAGE. Applicants have found that the chemotactic factor of the present invention induces cell migration.

Amended claim 8 of the present invention is as follows:

> 8. A chemotactic factor extractable by saline from precementum and/or cementum of a Mammalian tooth comprising a purified gingival fibroblast chemotactic factor having a molecular weight of 67000 ± 1000 measured by SDS-PAGE.

Applicant respectfully submits that Ogata et al. cannot anticipate the presently claimed invention because Ogata et al. does not teach a "purified gingival fibroblast chemotactic factor having a molecular weight of 67000 ± 1000 measured by SDS-PAGE."

Ogata et al. is directed to extracts from cementum, bone dentin and enamel obtained using 4 M guanadine HCL ("G Extract") or 4 M guanadine HCl/0.5 M EDTA ("E Extract") and the chemotactic properties of these extracts. (See Ogata, Abstract). These extracts do not appear as a single band with a molecular weight of 67 ± 1 kDa on SDS-PAGE as in the present invention. Rather, referring to Fig. 1 of **Ogata et al.**, the SDS-PAGE of the G extracts show a smear of proteins from well above a weight of 94 kilodaltons to below 43 kilodaltons in contrast to Figure 4 of the present invention which do not show such smears. Fig. 2 of **Ogata et al.** shows two-dimensional gels further showing a heterogeneous mix of proteins.

Thus, while the present invention is directed to a "purified gingival fibroblast chemotactic factor having a molecular weight of 67000 ± 1000 measured by SDS-PAGE," Ogata is directed only to G and E extracts that are a smear of proteins from below the 43 kD range to above 94 kD. Further, nothing in Ogata et al. teaches or suggests which of the various constituents of the G Extracts is/are responsible for the chemotactic property of the G Extract and nothing in Ogata provides any structural characteristics of the chemotactic constituents of the G Extract. Further, Ogata et al. do s not provid any method for obtaining or isolating the constituents

of the compositions that have chemotactic properties. Thus, Ogata does not provide teach or suggest the purified CCTF of present claim 8.

The Office's rejection under 35 U.S.C. § 102(b) is predicated on the presumption that a 67 kd band in the G extract of Ogata would, if purified, be the same CCTF factor claimed by Applicant. In fact, there is abundant evidence that the present claimed chemotactic factor is not the same as the chemotactic factors described by Ogata et al. This evidence is as follows:

1. Ogata et al. teaches that the biological source material is first extensively washed with saline, and following this wash, a strong denaturing agent (guanidine) is used to elute the chemotactic factors from the remaining bovine materials. In contrast, the chemotactic factor of the present invention is readily eluted by saline alone. As such, Applicant believes that the vast majority of the presently claimed CCTF would have been likely washed off before extraction in the methods of Ogata et al.

2. In Ogata et al., the "G" extract chemotactic factors from cementum do not bind to DEAE. Conversely, the saline extracted cementum factors of the present invention are purified by binding to DEAE and then to hydroxyapatite.

3. Ogata et al. show that their "G" extract chemotactic factors are heat labile (see Fig. 4). On the other hand, the present invention teaches that the purified chemotactic factor is not inactivated by heat treatment (see page 13, second paragraph from the bottom).

Thus, Applicant believes based on Item (1) above, that the present claimed CCTF would not be present in the G Extract of Ogata et al. Items (2) and (3) further indicate that the factors are different because they have different binding properties and different heat lability. Since the two compositions are made by processes that would appear to be mutually exclusive and the two compositions have completely different properties, Applicant respectfully submits that the Office cannot conclude that the G Extract, or any constituent thereof, renders the presently claimed invention anticipated. Withdrawal of the rejection and allowance of claims 8 is respectfully requested.

Claims 9-12 depend from claim 8 and are patentable for at least the same reasons as claim 8. Withdrawal of the rejection and allowance of claims 9-12 is respectfully requested.

Double Patenting

Claims 8, 10 and 12 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2b [*sic*] and 3 of U.S. Patent No. 6,429,193. In response, a terminal disclosure is filed herewith. Withdrawal of the rejection is respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6810 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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Date: March 19, 2003

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Version with markings to show changes made:

IN THE SPECFICATION

The paragraph at p. 5, lines 4-13:

The present inventors have studied about already-known cell adhesion and cell growth factors to solve the above problems, but [brought no good solution] these prior factors were inadequate. Therefore, [they] the present inventors have further studied and found that precementum and/or cementum of a tooth of Mammalia contains a substance which has a chemotactic activity and causes invasion, growth and differentiation of cells capable of adhering new connective tissue, thereby to attract the cells to connective tissue.

The paragraph at p. 5, lines 14-24:

The present inventors have also found that a novel chemotactic factor (hereinafter referred to as CCTF) can be purified by immersing precementum and/or cementum collected from extracted [a] tooth of Mammalia in saline or collagenase-containing saline with stirring to obtain an eluted ingredient, and subjecting the eluted ingredient to molecular weight fractionation, ion-exchange adsorption chromatography and hydroxyapatite adsorption chromatography. Thus, the present invention has been completed.

The paragraph at p. 11, line 7 - p. 12, line 5:

First, periodontal ligament fibers of forty bovine teeth extracted from butchered bovines were removed [not remaining] using a scaler. Then, cementum containing precementum was scraped using a scaler and dispersed in 20 ml of saline (pH 7) containing 1% collagenase. After the dispersion was stirred using Voltex (Automatic Mixer S-100, manufactured by Taiteck Co.) for 10 minutes, a protein ingredient was eluted. Furthermore, the insoluble matter was removed by centrifugal separation at 3000 rpm for 5 minutes to obtain a supernatant. Then, the supernatant was filtrated through a membrane filter having a pore diameter of 0.22 μ (Durapore, manufactured by Nippon Milli pore Co.) and the filtrate was

concentrated to 4 ml (11 mg of a protein content measured by Bradford's process). Preparative columns TSK G3000 (2.15 cm in inner diameter X 60 cm in length, manufactured by Toso Co.) and TSK G4000 (2.15 cm in inner diameter X 30 cm in length, manufactured by Toso Co.) were connected each other in series, and then the molecular weight fractionation was conducted by HPLC gel filtration chromatography.

The paragraph at p. 17, line 8 (lines counted by not including Table 1) - p. 12, line 5:

First, periodontal ligament fibers of forty bovine teeth extracted from butchered bovines were removed [not remaining] using a scaler. Then, cementum containing precementum were scraped using a sharp scaler and dispersed in 20 ml of saline (pH 7) containing 1% collagenase. After the dispersion was stirred using Voltex (Automatic Mixer S-100, manufactured by Taiteck[.] Co.) for 10 minutes, a protein ingredient was eluted. Furthermore, the insoluble matter was removed by centrifugal separation at 3000 rpm for 5 minutes to obtain a supernatant. Then, the supernatant was filtrated through a membrane filter having a pore diameter of 0.45 μ (Durapore, manufactured by Nippon Milli pore Co.) and the filtrate was concentrated to 4 ml using an [ultrafilteration] ultrafiltration membrane having a fractionated molecular weight [is] of 200,000.

IN THE CLAIMS

8. (Amended) A [purified gingival fibroblast] chemotactic factor [(CCTF)] extractable by saline from precementum and/or cementum of a Mammalian tooth[,] [the] comprising a purified gingival fibroblast chemotactic factor [consisting essentially of a factor with] having a molecular weight of 67000 ± 1000 measured by SDS-PAGE.

9. (Amended) The [purified gingival fibroblast] chemotactic factor [(CCTF)] according to claim 8, [which] wherein the gingival fibroblast chemotactic

factor is glycosylated[,] and has an amino acid composition of: Asp 10.6 ± 0.5%, Thr 3.7 ± 0.3%, Ser 13.3 ± 0.7%, Glu 13.8 ± 0.7%, Gly 23.3 ± 1.2%, Ala 10.1 ± 0.5%, Cys/2 3.6 ± 0.3%, Val 6.7 ± 0.3%, Ile 3.8 ± 0.3%, Leu 7.3 ± 0.4% and Lys 3.8 ± 0.3%, and has an isoelectric point of 6.5 ± 0.5.

10. (Amended) The [purified gingival fibroblast] chemotactic factor [(CCTF)] according to claim 8, wherein the Mammalian is a bovine.

11. (Amended) The [purified gingival fibroblast] chemotactic factor [(CCTF)] according to claim 9, wherein the Mammalian is a bovine.

12. (Amended) A drug for accelerating adhesion of new connective tissue, comprising the [precementum- and/or cementum-derived] purified gingival fibroblast chemotactic factor [(CCTF)] obtained from precementum or cementum of any one of claims 8 to 11 as an active ingredient.[.]